UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/899,303 | 07/06/2001 | Geert Maertens | 2752-52 | 3515 |

23117 7590 04/21/2003

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | 18 |

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/899,303 | MAERTENS ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *67-96* is/are pending in the application.

4a) Of the above claim(s) *71,72,78,80-84 and 92-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-70,73-77,79,85-91,95 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11 & 16* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *18* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Preliminary amendments filed on 12/12, 2001, 08/26/2002 and 01/07/2003 are all acknowledged. Claims 1-66 have been canceled. Claims 67-96 are added. Claims 67-96 are pending.

### *Election/Restrictions*

1. Applicant's election with traverse of Group I, claims 67-77, 79, 85-91and 95-96 in the scope of Vaccian vector encoding HCV envelope protein, preferably SEQ ID NO: 7 in Paper No. 14 and 17 is acknowledged. The traversal is on the ground(s) that it would not constitute a serious burden to search all sequences except SES ID NO 29 and 31 because all other claimed polypeptide or SEQ ID Nos represent peptides of the single HCV polypeptide derived from a single genome sequence of same single HCV isolate of type 1b. This is not found persuasive because an HCV genome constitutes about 9 structural and non-structural proteins; each of them has different molecular and functional characteristics. It is unclear what the structural relationship between each claimed sequences.

2. Regarding to the argument about all vector should be examined, Applicants are reminded that each kind of vector has different structure and function. They exhibit different patentable weights and constitute distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

To reflecting the examination on the scope of a vaccina vector carrying an HCV E1 protein, preferably SEQ ID NO: 7, claims 67-70, 73-77, 79, 85-88 and 95-96 are considered before the examiner.

Applicants are reminded to amend the claims in the scope of Vaccian vector encoding HCV envelope protein, preferably SEQ ID NO: 7 for reflecting the examination on the merits and cancel claims 71-72, 78 and 92-94 drawn to the non-elected groups.

### *Information Disclosure Statement*

3. The information disclosure statement filed 07/06/2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not

been considered. In particular, Office cannot make any copies according to the information provided for the foreign patent documents even after searching the parental applications .

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 67-70, 73-74, 76-77, 79 and 85-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 67 is vague and indefinite in that the metes and bounds of a nucleotide sequence are not defined. The family of HCV virus has many serotypes/isolates and each of them may have different sequence structure since HCV is a RNA virus, which tends to mutate consistently. If Applicants wish to claim a particular sequence, please amend the claim to a particular sequence with a defined SEQ ID NO. This affects the dependent claims 68-70, 73-74, 76-77, 79 and 85-86.

7. Claims 58-70 are confusing because the orientation of HCV E1 protein is unclear. According to Fields et al. (Virology, Third edition, 1995, page 1037), the HCV E1 polypeptide starts from amino acid residue 191/192 and ends with 383/384, it is unclear where does the position 1 of claimed HCV E1 start with. If the vector only comprises the nucleic acid sequence that encodes the HCV E1 protein, it only has amino acid residues from 191/192 to 383/384, how does the clamed E1 protein end with position beyond 383/384. Please clarify.

8. Claims 75, 95 and 96 are vague in that the metes and bonds of the recited "a parts thereof" are not defined. Is 10 amino acids are parts thereof? Or 50 amino acid residues belong to the parts thereof? The claims are interpreted in light of the specification; however, the specification does not teach what the definition of "parts thereof" is. Therefore, the claims are considered indefinite.

9. Claim 85 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: the dosage of immunization, the rout of immunization and what kind of immune response is induced etc.

***Claim Rejections - 35 USC § 112***

10. Claim 85 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial, asserted utility or a well-established utility.

11. In the instant case, the specification only teaches how to express deferent fragment of HCV E1 protein by a recombinant vector. However, the immunogenicity of each E1 fragment expressed by the recombinant vector is not tested. Moreover, state of art teach that HCV vaccine has been tried with several HCV proteins, such as envelope glycoprotein E1, E2 and nucleocapsid protein C, but there is no demonstration of successes for any of them. The development of HCV vaccine is extremely unpredictable because (1). Heterogenecity of HCV E1 protein among different HCV genotypes as evidenced by Bukh et al. (P.N.A.S. USA 1993, Vol. 90, pp. 8234-8238) since HCV is a RNA virus, which tends to mutate consistently, and so far, there is no HCV antibody has been approved as a reutilizing antibody that is able to protect HCV infection; (2). A relative week immune response to the HCV antigen; and (3). Neutralizing antibody response to HCV has been difficulty to assess. In general, in filed of HCV vaccine development, in order to prove the efficacy of an HCV vaccine, large primates, such as chimpanzees, but not just small animal models are required (see detail discussion by Hsu et al. (Clinics in Liver disease 1999, Vol. 3, pp. 901-915). Therefore, a utility of using the claimed vector carrying an E1 fragment requires further research to identify which fragment carried by the vector can be used to immunize human to prevent HCV infection. A general assumption of using the vector to immunize human cannot be established even in view of the state of art.

12. Claim 85 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112***

13. Claims 67, 79 and 85 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expressing an HCV E1 protein fragment by using a recombinant vaccinia viral vector, does not reasonably provide enablement for a method for using the vector to immunize human to protect HCV infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) & 2) State of art & Unpredictability of the filed. HCV vaccine has been studied with several HCV encoded proteins, such as envelope glycoprotein E1, E2, nucleocapsid protein C, non-structural protein NS3mn, NS4, and NS5 and combination thereof. However, none of these vaccine compositions have been approved to be successfully used for immunizing human from HCV infection. The development of HCV vaccine is extremely unpredictable because the following problems:

(1). The asymptomatic or inconsistent of HCV infection make it hard to assess any effective remedy in the clinic, (2). High heterogenecity of HCV E1 protein among different HCV genotypes as evidenced by Bukh et al. (P.N.A.S. USA 1993, Vol. 90, pp. 8234-8238) since HCV is a RNA virus, it tends to mutant consistently, (3). Neutralizing antibody response to HCV has been difficulty to assess, (4). A relative week immune response to the HCV antigen. (5). In order to prove an HCV vaccine, a large primate, such as chimpanzees rather than a small animal models, are required (See detail discussions by Hsu et al. Clinics in Liver disease 1999, Vol. 3, pp. 901-915 and Dr. Robert Purcell (Hepatology 1997, Vol. 26, pp. 11S-14S).

3) &4). Number of working examples and Amount of guidance. The specification only teach how to express recombinant E1 protein fragment by using a recombinant vector, there is no teach

for using the protein expressed by the vector to immunize an human to protect HCV infection. The specification even does not teach what kind of immunity that the vector carrying a E1 fragment of HCV would produce in an animal model.

5) Scope of the claims. The claims broadly read on a method for using the claimed vector expressing an HCV E1 protein to immunize human.

6) & 7) Nature of the invention and technical requirement within level of skill in the art. The invention involves one of the most complex and unpredictable fields of developing HCV vaccine. Therefore, the level of the skill in art is very high. As noted by some of the preeminent researchers on HCV (i.e. Hsu et al., and Dr. Rober Purcell), the significant hurdles remain to be overcame in order for the skilled artisan to practice successful the full scope of the claimed invention.

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention.

### *Claim Rejections - 35 USC § 102*

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 67-68, 75, 87 and 95-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuura et al. (J. Virol. 1992, Vol. 66, pp. 1425-1431)

17. Claims 67-68, 73, 75, 87 and 95-96 are interpreted as a recombinant life vector carrying a nucleotide of HCV starting with amino acid position 1-192 and ending with amino acid position 250-400, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably comprising the SEQ ID NO: 7 or part of SEQ ID NO: 7. The

starting point of the nucleotide position is interpreted from the positions 1 and 192 of the HCV genome.

18. Matsuura et al. teach a recombinant live eukaryotic vectors comprising a nucleotide sequence of HCV, wherein some of the fragments start with the position 1 to position 155 and end with position 342. Nevertheless, all inserted fragments allow the expression of an HCV E1 as a single envelope viral protein with 35 kDa under a viral promoter SRα, wherein some of the E1 fragment in the recombinant vector starting from the amino acid residue 1, and ends at 340 that contains part of the claimed amino acid sequence of SEQ ID NO: 7 (see entire document, especially Fig. 1 and lines 50-65 on the 2nd column of page 1426). Therefore, the claimed invention is anticipated by Matsuura et al.

19. Claims 67, 75, 87 and 95-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Hijikata et al. (P.N.A.S. USA, 1991, Vol. 88, pp. 5547-5551).

20. Claims 67, 73, 75, 87 and 95-96 are interpreted on its broad scope as a recombinant life vector carrying a nucleotide of HCV, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably as SEQ ID NO: 7 or part of SEQ ID NO: 7.

21. Hijikata et al. teach a recombinant live eukaryotic vectors comprises a nucleotide sequence of HCV, which allowing the expression of an HCV E1 as a single envelope viral protein with 35 kDa under a prokaryotic promoter T7 (see entire document, especially Fig. 1 on page 5548 and Fig. 3 on page 5549), wherein E1 sequence is a part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by Hijikata et al.

22. Claims 67, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohara et al. (J. Gene. Virol. 1992, Vol. 73, pp. 2313-2318).

23. Kohara et al. teach a recombinant live eukaryotic vaccinia vector carrying an HCV E1 protein fragment, which allowing the expression of an HCV E1 as a single envelope viral protein (see entire document, especially Fig. 4&5 on page 2316), which contains part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by cited prior art.

24. Claims 67, 75, 87 and 95-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Hsu et al. (Hepatology 1993, Vol. 17, pp. 763-771).

25. Hsu et al. teach a recombinant live eukaryotic vector carrying an HCV E1 protein fragment, which allowing the expression of an HCV E1 as a single envelope viral protein (see entire document, especially Fig. 1 on page 764 and Fig. 4 on page 767), which comprising the part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by cited prior art.

26. Claims 67-68, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Devare et al. (EP 472 207A2).

27. Devare et al. teach a recombinant live vector CKS comprising the putative envelope region of HCV from amino acids 114-469, which is just in the region of claimed HCV E1 starting from position of 1 and 192 and ends with amino acid residue 250-400 (See section of G on col. 35 of page 20), which contains part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by cited prior art.

***Claim Rejections - 35 USC § 102***

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

29. Claims 67-70, 73, 75, 87 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Lanford et al. (Virology 1993, Vol. 197, pp. 225-235).

30. Claims 67-70, 75, 87 and 95-96 read on a recombinant life vector carrying a nucleotide of HCV, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably comprising the SEQ ID NO: 7 or part thereof. The starting point of the amino acid residue is interpreted from the positions 1 and 192 of the HCV genome, wherein the nucleic acid sequence comprises operably linked ATG codon at the 5'-terminal and a stop codon at the 3'-terminal at the C-terminal and further a 3-10 histidin codon at the Xa cleavage site of 3'-terminal.

31. Lanford et al. teach a recombinant live eukaryotic virus vector, carrying an HCV E1 protein fragment encoding HCV amino acids 117-386 or 117-340, in which a carboxyl terminal was truncated at residue 340 to remove a carboxyl terminal hydrophobic domain. The 5' of

inserted HCV cDNA fragment contains an ATG for initiation site and the 3' contains a TAA termination codon. The expressing vector allows the expression of an HCV E1 as a single envelope viral protein. (See entire document, especially Fig. 6 on page 230 and Fig. 7& 8 on page 231), which contains part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by cited prior art.

32. Claims 67, 73, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Chien et al. (WO 94/01778A1).

33. Chien et al. teach a recombinant live vector including vaccinia vector (Claims 1-7) carrying an HCV E1 protein fragment encoding HCV amino acids. The expressing vector allows the expression of an HCV E1 as a single envelope viral protein (See entire document), which contains part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by cited prior art.

34. Claims 67, 73, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Ralston et al. (J. Virol. 1993, Vol. 67, pp.6753-6761).

35. Ralston et al. teach a recombinant live eukaryotic vaccinia vector, carrying an HCV sequence, which allows the expression of an HCV E1 as a single envelope viral protein. (See entire document, especially Fig. 4 on page 6758), which contains part of SEQ ID NO: 7 or part thereof. Therefore, the claimed invention is anticipated by cited prior art.

36. Claims 67, 73, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Grakoui et al. (J. Virol. 1993, Vol. 67, pp. 1385-1396)

37. The claimed invention read on a recombinant life vaccinia vector carrying a nucleotide of HCV, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably, SEQ ID NO: 7 or part of SEQ ID NO: 7.

38. Grakoui et al. teach a recombinant live eukaryotic vaccinia vector carrying an HCV E1 protein fragment, for example, pET-3xa/HCV 236-382, which allowing the expression of an HCV E1 as a single envelope viral protein under a promoter T7, wherein some of the E1 fragment in the recombinant vector starting from the amino acid residue 236 and ends with 382 of a putative HCV E1 protein sequence, which contains part of SEQ ID NO: 7 (see entire document, especially Fig. 1 on page 1386). Therefore, the claimed invention is anticipated by cited prior art.

39. Claims 67-68, 73, 75, 87-88 and 95-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Ray et al. (J. Virol. 1994, Vol. 68, pp. 4420-4426),

40. The claimed invention read on a recombinant life vaccinia vector carrying a nucleotide sequence of HCV starting from position 1 and ending with position between 290-400, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably, SEQ ID NO: 7 or part of SEQ ID NO: 7.

41. Ray et al. teach a recombinant vaccinia viral vector that is used for expressing a the structural proteins of HCV E1 protein fragment ranging from amino acid residues 1-339 (v9AV/CE1), which contains part of SEQ ID NO: 7. Therefore, the claimed invention is anticipated by the cited reference.

***Claim Rejections - 35 USC § 102***

42. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

43. Claims 67-70, 75, 87, and 95-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Watanabe et al. (US Patent No. 5,610,009A).

44. Claims 67-70, 75, 87, and 95-96 are interpreted as a living recombinant vector carrying a fragment of HCV E1 protein, wherein the E1 protein fragments range from 192-400, more particularly end in the region between positions 250-341. Furthermore, the E1 protein contains a

deletion in which the hydrophobic domain of amino acid residues between positions 264-293, plus or minus 8 amino acids (272-301 for plus amino acids or 256-285 for minus 8 amino acids by calculation or 256-301 by adding 8 amino acids at the 5' and minus 8 amino acid at the 3' or 242-350 vice versa), preferably, the E1 is SEQ ID NO: 1 or part thereof.

45. Watanable al. teach a recombinant live eukaryotic adenovirus vector carrying deferent fragments of HCV E1 protein. Some of them start with the amino acid position 192 originated from the whole genome of HCV cDNA and ends with amino acids 259 or 337 or 383 (See lines 16-29 on col. 12), in which a carboxyl terminal was truncated at residue 260-296 to remove the internal hydrophobic region that is the claimed region between positions 264-293, plus or minus 8 amino acids, which is part of SEQ ID NO: 7 . Therefore, the claimed invention is anticipated by the cited reference.

46. Claims 67-68, 75, 87 and 95-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Brechot et al. (US Patent No. 5,879,904A).

Brechot et al. disclose a live vector carrying different fragments of HCV E1 with different ranges (See lines 65 on col. 1 to line 25 on col. 2 and lines 27-29 on col. 7 and claim 5), which contains part of claimed SEQ ID NO: 7. Therefore, the claimed invention is anticipated by the cited reference.

***Claim Rejections - 35 USC § 103***

47. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

48. Claims 67-70, 73-75, 87-88 and 95-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanford et al. (Virology 1993, Vol. 197, pp. 225-235), Ralston et al. (J. Virol. 1993, Vol. 67, pp.6753-6761), Watanabe et al. (US Patent No. 5,610,009A) and Ford et al. (Protein expression and purification 1991, Vol. 2, pp. 95-107).

49. Claims 67-70, 73, 75, 87-88 and 95-96 read on a recombinant life vector carrying a nucleotide of HCV, which allows the expression of an HCV E1 protein as a single or specific oligomrized envelope protein, more preferably comprising the SEQ ID NO: 7 or part of SEQ ID NO: 7. The starting point of the amino acid residue is interpreted from the positions 1 and 192 of the HCV genome, wherein the nucleic acid sequence comprises operably linked ATG codon at the 5'-terminal and a stop codon at the 3'-terminal at the C-terminal and further a 3-10 histidin codon at the Xa cleavage site of 3'-terminal. Furthermore, the E1 protein contains a deletion in which the hydrophobic domain of amino acid residues between positions 264-293, plus or minus 8 amino acids (272-301 for plus amino acids or 256-285 for minus 8 amino acids by calculation or 256-301 by adding 8 amino acids at the 5' and minus 8 amino acid at the 3' or 242-350 vice versa),

50. Lanford et al. teach a recombinant live eukaryotic vaccinia vector, carrying an HCV E1 protein fragment encoding HCV amino acids 117-386, in which a carboxyl terminal was truncated at residue 340 to remove a carboxyl terminal hydrophobic domain. The 5' of inserted HCV cDNA fragment contains an ATG for initiation site and the 3' contains a TAA termination codon. The expressing vector allows the expression of an HCV E1 as a single envelope viral protein. (See entire document, especially Fig. 6 on page 230 and Fig. 7& 8 on page 231), which contains part of SEQ ID NO: 7. Lanford does not teach to use vaccinia viral vector and add 3-10 histidin codon at factor Xa site of the C-terminal.

51. Regarding to claim 88 of using vaccinia viral vector, it is well know in the art that vaccinia vector can be used for expressing a recombinant protein if the sequence of the protein or polypeptide is known. For example, Ralston et al. teach to use a vaccinia viral vector for expressing HCV E1 protein (See entire document).

52. Regarding the addition a histidin codon at the C-terminal of claim 74, it is well know in the art that addition of a tag, such as histidin tag has been used as routine for the purpose of purification of a fusion protein as evidenced by Ford et al. which is a powerful technique based on interactions of some proteins with immobilized transition metal ions. They particularly teach that the technique is involved by adding poly(his) tails ranging in length from 2 to 6 residues and fused to either the N-terminus or C-terminus (See section of 7 Poly(His) Tails on page 100),

therefore, it greatly benefit for the purification process by using a metal affinity chromatography (IMAC).

53. Regarding to the limitation of claim 70 that HCV E1 protein contains a deflection at the amino acid sequence between the position of 264-293, plus or minus 8 amino acids (272-301 for plus amino acids or 256-285 for minus 8 amino acids), Watanable al. teach a recombinant live eukaryotic adenovirus vector carrying deferent fragments of HCV E1 protein. Some of them start with the amino acid position 192 originated from the whole genome of HCV cDNA and ends with amino acids 337 or 383 (See lines 16-29 on col. 12), in which a carboxyl terminal was truncated at residue 260-296 to remove the internal hydrophobic region, which is within the claimed region between positions 264-293, plus or minus 8 amino acids ..

54. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to combine the disclosures taught by Lanford et al. Ralston et al. Watanable et al. and Ford et al. to make a recombinant vector for expressing an HCV E1 protein fused with a histadin tails at its C-terminal and further containing a truncation in the hydrophobic domain as taught by Watanable et al. with highly expected result. As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

55. No claims are allowed.

***Conclusion***

Claims 70, 76 and 77 are deem free of art given failure of the prior art to teach or reasonably suggest a recombinant vector for expressing a recombinant E1 protein, in which the glycosylation sites have been removed at the nucleic acid level.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li April 11, 2003

JAMES HOUSEL 4/21/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600